SHORT REPORT

Angiotensin-converting enzyme inhibitor fetopathy: long-term outcome

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Fetal exposure to angiotensin-converting enzyme inhibitors (ACEIs) is associated with increased neonatal morbidity and mortality. Long-term follow-up of three patients with fetal ACEI exposure revealed impaired renal function in two, severe hypertension and proteinuria in one and isolated polycythaemia in all three. Careful long-term follow-up of children with ACEI fetopathy is recommended.

Angiotensin-converting enzyme inhibitors (ACEIs) are commonly used antihypertensive drugs in children and adults. Fetal exposure to ACEIs and angiotensin receptor antagonists is associated with fetal and neonatal morbidity and mortality including oligohydramnios, growth retardation, hypocalvaria, premature birth, pulmonary hypoplasia with respiratory distress and acute renal failure.[1] However, there is limited knowledge about long-term outcomes.[2]

The pathogenetic mechanisms of renal disease in affected fetuses and neonates are not fully understood. Histologically there is tubular dysgenesis and acute tubular necrosis. Recently published studies have shown considerable evidence that inhibition of the renin–angiotensin system leads to severe, chronic low perfusion pressure in the fetal kidney, resulting in acute renal failure in the neonate.[3]

We describe the long-term outcomes in three children after fetal exposure to enalapril.

PATIENTS AND METHODS

The local ethical committee approved the study.

Our patients were two girls (A, B) and one boy (C) exposed to the ACEI enalapril during the third trimester of pregnancy. None of the mothers had primary renal disease. After initial treatment in the neonatal intensive care unit, the patients were regularly followed up in our outpatient clinic.

At the age of 18.1 years (A), 12.8 years (B) and 6.4 years (C) the following variables were evaluated: growth, renal function (glomerular filtration rate (GFR) estimated by the local Schwartz formula (40 × body length in cm/plasma creatinine in μmol/l)), 24-h ambulatory blood pressure, 24-h proteinuria and renal ultrasound findings.

Table 1 Fetal and neonatal course of three patients with fetal exposure to enalapril

	Patient		
	A	B	C
Enalapril dosage, mg	340	330	230
Duration of pregnancy, weeks	35	36	39
Birth weight, g (centile)	2100 (50)	1975 (25)	3175 (50)
Anuria, days	7	3	7
Creatinine, μmol/l (maximal/at 3 months)*	537/56	464/42	691/49
Treatment	Dialysis	Furosemide	Furosemide
Blood pressure, mm Hg	70/50	65/30	70/40

*Creatinine measured by the Jaffé method.

RESULTS

Fetal and neonatal course (table 1)

The fetal course was uneventful, without oligohydramnios. Two patients were born preterm, none had respiratory distress, but all developed transient acute renal failure. Renal ultrasound showed two normal-sized kidneys with hyperechogenic cortex. Renal biopsy revealed tubular dysgenesis in patient A.

Long-term course (table 2)

Patient A

Patient A was found to have hypertension at the age of 10 years. Mild renal failure with proteinuria developed at 14 years. Despite triple medication, blood pressure remained elevated. Magnetic resonance angiography showed a small scar but normal vasculature, allowing additional treatment with ACEIs. Current treatment consists of angiotensin II receptor antagonist (losartan 2 mg/kg/day), hydrochlorothiazide (0.5 mg/kg/day), nifedipine (1 mg/kg/day) and atenolol (2 mg/kg/day) resulting in blood pressure ⩽95th centile.

A rise in erythrocyte count and haemoglobin concentration was first observed at 5 years of age. At 16 years, bone marrow aspiration and molecular analysis of the erythropoietin receptor and the von Hippel–Lindau gene showed normal findings; however, serum erythropoietin concentration was low. So far, five phlebotomies (500 ml each) have been done.

Table 2 Long-term outcome in three patients with fetal exposure to enalapril

	Patient		
	A	B	C
Age, years	18.1	12.8	6.4
GFR, ml/min/1.73 m^2*	60	96	64
24-h proteinuria, g	1.5	<0.06	0.18
Renal ultrasound†	Small, bright kidneys	Normal	Small, bright kidneys
24-h ABPM MAP, mm Hg‡	100 (non-dipper)	77 (non-dipper)	76 (dipper)
Haemoglobin, g/l§	182	152	150
Erythrocytes T/l (normal <5)	6.2	5.0	5.6
Erythropoietin U/l (normal 8–22)	<5	10	8.7

ABPM, ambulatory blood pressure; GFR, glomerular filtration rate; MAP, mean arterial pressure.
*Normal >80ml/min/1.73 m^2.
†''Small'' indicates renal length < height related third centile.
‡MAP, 95th centile: 97 (A, B), 87 (C).
§Normal <160 g/l (A, B), <140 g/l (C)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; GFR, glomerular filtration rate

What is already known on this topic

- Long-term data on children with fetal exposure to angiotensin-converting enzyme inhibitors are scarce, with only one case report published so far.

What this study adds

- Long-term follow-up of fetal exposure to angiotensin-converting enzyme inhibitor revealed marked impairment of renal function. Thus, careful and regular monitoring is mandatory in children with ACEI fetopathy.

Patient B

Blood pressure and renal function have always been normal. At 12 years, mild, isolated polycythaemia with low-normal concentrations of serum erythropoietin was noted.

Patient C

Blood pressure has always been normal. However, since 3 years of age renal function has shown a moderate decline with steadily rising plasma concentrations of creatinine (GFR 58 ml/min/1.73 m^2), associated with mild proteinuria and isolated polycythaemia with low-normal erythropoietin serum concentration.

DISCUSSION

Fetal exposure to ACEIs is associated with the risk of fetal and neonatal morbidity and mortality.[1] In our small series, all three children with ACEI fetopathy had neonatal acute anuric renal failure, with recovery of renal function within three months. However, over the years, two of the three children have developed progressive renal impairment, hypertension and proteinuria. It remains unclear whether ACEI dosage, duration of anuria or need of dialysis are prognostic factors.

Data on long-term outcomes in children with ACEI fetopathy are scarce.[2] A 14-year-old girl presented with reduced GFR, proteinuria and normal casual blood pressure. Renal biopsy showed enlarged, hypertrophic glomeruli and focal tubular dilatation, assuming compensatory hypertrophy due to reduced number of nephrons. The net result of reduced renal mass in association with fetal and early life events could lead to adult chronic renal disease.

The pathogenetic mechanisms of ACEI fetopathy are not fully understood. It has been suggested that developmental abnormalities of proximal tubules are caused by primary (or acquired) defects in genes that encode factors involved in tubular growth and differentiation.[4 5] Angiotensin II acts as a growth factor for proximal tubular cells in vitro and stimulates tubular development during normal growth in utero.[5]

Evidence has emerged that in humans, hypoperfusion of the fetal kidney is the key mechanism.[3] The loss of proximal tubule differentiation and the renal tubular dysgenesis phenotype have been observed in several conditions resulting in fetal kidney hypoperfusion—for example, twin-twin transfusion syndrome, major cardiac malformations and severe liver disease.[3] In these conditions the renin–angiotensin system is upregulated. Mutations in genes in the renin–angiotensin system (*angiotensinogen*, *renin*, *angiotensin converting enzyme*, *angiotensin type I receptor*) cause renal tubular dysgenesis.[3] These observations suggest that the common feature in utero in acquired (eg secondary to ACEI) and inherited renal tubular dysgenesis is low perfusion pressure of the kidneys, leading to neonatal acute renal failure. An unexpected finding in all our patients was isolated polycythaemia. As the serum concentration of erythropoietin was low or in the low-normal range, other mechanisms for increased stimulation of erythropoiesis have to be considered.

In summary, long-term observation of children with ACEI fetopathy revealed marked impairment of renal function. Thus regular follow-up of such children is mandatory. The relationship between polycythaemia and fetal exposure to ACEI remains unclear.

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